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A1

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Published
With international search report.

(54) Title: VETERINARY COMPOSITION CONTAINING A PROTON PUMP INHIBITOR

(57) Abstract

A stable, oral pharmaceutical composition comprising a proton pump inhibitor and a gelling agent designed for the treatment of gastric acid related diseases in animals, the process for preparation of the composition and the use thereof.

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Veterinary composition containing a proton pump inhibitor.

Technical Field

The invention relates to an oral pharmaceutical composition comprising a proton pump inhibitor (PPI) and is designed for the treatment of gastric acid related diseases in animals.

Background of the Invention

Proton pump inhibitors are potent inhibitors of gastric acid secretion and are used for the treatment of gastric acid related diseases in humans, such as for instance gastric and duodenal ulcers. These substances are susceptible to degradation/transformation in acid reacting and neutral media. Pharmaceutical formulations for oral administration to humans are preferably enteric-coated. These formulations are sensitive to moisture and must be stored in well-closed, tight containers during long-term storage.

Peptic ulcer diseases are common also in some animals, especially in horses and camels. Other animals of interest for treatment of peptic ulcer diseases are for example dolphins, sea-lions, llamas, dogs, cats and pigs. By gastro-endoscopic evaluation of horses, ulcers have been found in the squamous mucosa, the non glandular fundus, the glandular stomach and the duodenum. The aetiology of gastro-duodenal ulcers in the equine species is mainly unknown but stress appears to play an important role in some cases.

Anti-ulcer compounds such as for instance histamine-2-receptor antagonists have reportedly been administered several times a day to horses by oral or naso-gastric tubes. This procedure can be traumatic and may require light sedation of the horse. Trained persons are required for the administration.

Omeprazole and other proton pump inhibitors are potent inhibitors of gastric acid secretion in animals. They block the production of gastric acid by inhibition of H^+K^+-ATPase, the enzyme responsible for the production of hydrogen ions in the parietal cells. The proton pump inhibitors cause profound acid suppression and unlike most other anti-ulcer compounds such as for instance the H_2-blockers, omeprazole can be given once daily. According to the present invention enteric-coated beads containing omeprazole in a gel formulation can easily be applied onto the dorsal part of the tongue of the horse during field conditions and is well accepted by the horses.

Such a moist gel comprising enteric-coated beads of proton pump inhibitors is not stable during long-term storage at room temperature and must be prepared ex tempore. To-day there exist no such formulation on the market.

Omeprazole, 5-methoxy-2(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1H-benzimidazole, is disclosed in European patent no 5129 as a potent inhibitor of gastric acid secretion.

Lansoprazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]-1H-benzimidazole, is disclosed in European patent no 174 726 as a potent inhibitor of gastric acid secretion.

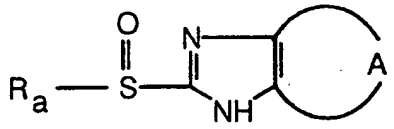
Pantoprazole is disclosed in European patent no 166 287 as a potent inhibitor of gastric acid secretion.

Leminoprazole is disclosed in UK patent no 2 163 747.

Detailed description of the invention

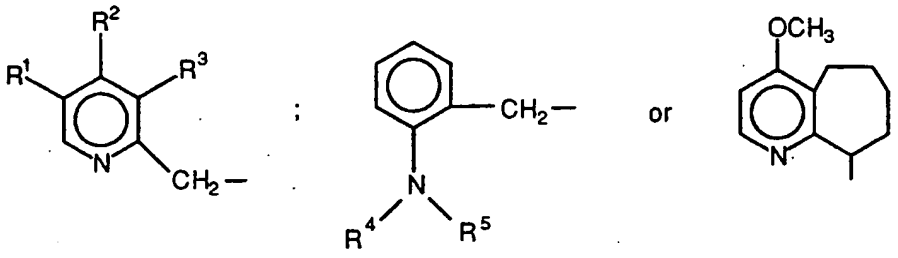
The object of the present invention is to provide oral pharmaceutical compositions for easy administration to horses and other animals. The proton pump inhibitor is in the form of dry particles, such as beads or tablets, which are coated with one or more coatings one of which is an enteric-coating. The beads or tablets can be prepared by compaction, crystallisation, applying a solution or suspension of the proton pump inhibitor onto inert cores, extrusion and spheronisation or similar processes. The enteric-coated beads or tablets are mixed with dry gelling agent(s), such as for instance xanthan gum, guar gum, locust bean gum, tragacanth, modified cellulose derivatives or similar gel forming compounds. When water is added to this mixture a paste-like gel is formed. The gel is for example applied dorsally at the tongue of the animal such as a horse with a suitable applicator.

Proton pump inhibitors used in the compositions of the invention are compounds of the general formula I



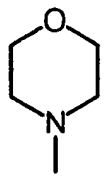
I

wherein R_a is



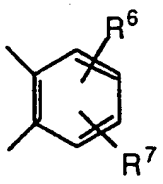
R^1 and R^3 are independently selected from hydrogen, lower alkyl, lower alkoxy

and halogen, R^2 is selected from hydrogen, lower alkyl, lower alkoxy, lower alkoxy-lower alkoxy, lower fluoralkoxy and



R^4 and R^5 are independently selected from lower alkyl,

A is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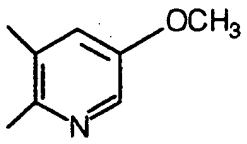
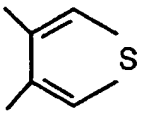
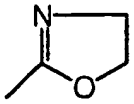

or


R^6 and R^7 are independently selected from hydrogen, lower alkyl, lower alkoxy, lower fluoroalkoxy, lower fluoroalkyl, halogen,

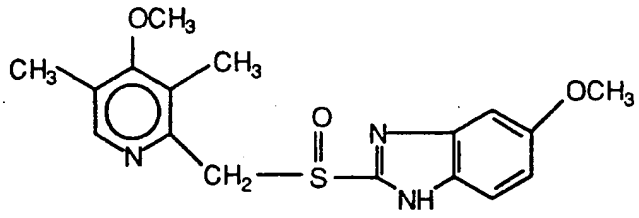

;


wherein R^8 is lower alkyl or lower alkoxy.

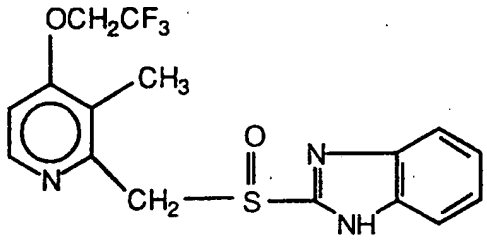
Lower alkyl in the present invention means an alkyl group having 1-5 carbon atoms.

Lower alkoxy in the present invention means an alkoxy group having 1-5 carbon atoms.

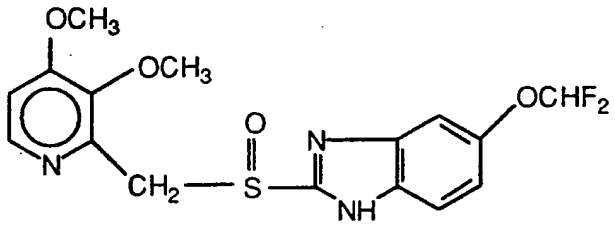
Examples of proton pump inhibitors according to formula I are



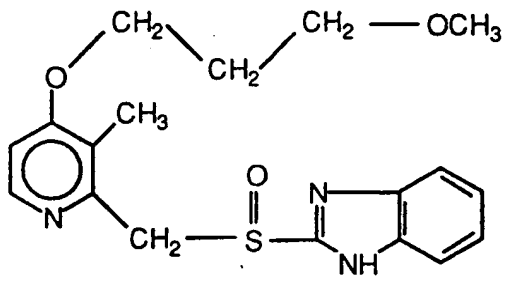
Omeprazole



Lanzoprazole



Pantoprazole



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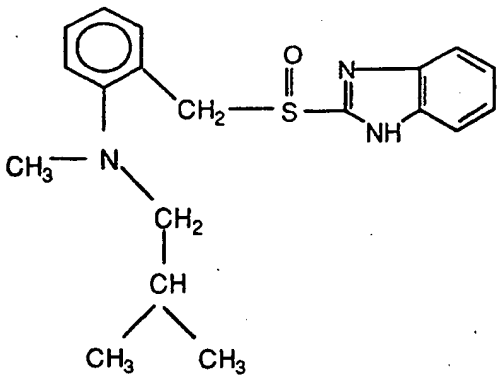
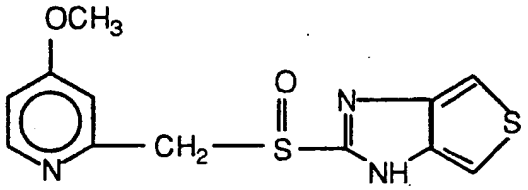


Leminoprazole



S— 4216

The proton pump inhibitors used in the compositions of the invention may be used in neutral form or in the form of a basic salt, such as for instance the Mg^{2+}, Ca^{2+}, Na^{+}, or K^{+} salts, preferably the Mg^{2+} of Na^{+} salts. Further where applicable, a compound listed above may be used in racemic form or in the form of a substantially pure enantiomer.

In one embodiment of the invention the enteric-coated particles are mixed with suitable substances, such as for instance suitable inorganic or organic water soluble salts of potassium, calcium, magnesium or aluminium. When a water solution of a suitable polymeric compound or compounds, such as for instance kappa-carrageenan, pectin, anionic polymers known to give gels with positively charged metal ions, or similar compounds, is added to the mixture a paste-like gel is formed through the interaction of the ions with the polymers.

In another embodiment of the invention the enteric-coated particles are mixed with

suitable constituents. When a low-viscous solution of a temperature-sensitive polymer, such as for instance ethylhydroxyethylcellulose (EHEC) or polyethylenepolypropylene glycols or similar substances, is added and the system is warmed to temperatures of 33-35°C or higher a viscous paste-like gel is formed.

In still another embodiment of the invention the enteric-coated particles are mixed with suitable substances in the form of gelforming agents, such as dry gelling agent. As gelforming agents can be used for example acacia, agar, alginic acid, sodium carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose or other similar cellulose derivatives, fucoidan, xanthan gum, furcellaran, laminaran or similar gelforming agents.

In a preferred embodiment of the invention the proton pump inhibitor is omeprazole.

The amount of the different components of the composition can vary and will depend on various factors such as for example the individual requirement of the animal treated.

The amount of gelforming agent can vary but is within the range 0.02-20% by weight calculated on the amount of wet gel, preferably in the range of 0.2-20% and especially 0.5-5% by weight.

The amount of active substance, i.e. the enteric-coated particles, depends on the individual dosages for the animal. For example the amount of enteric-coated particles is usually in the range of 0.1-20 grams, preferably 0.2-10 grams per dosage for horses. The total volume of the final gel given to horses is in the range of 5-50 ml.

Other suitable substances which may be incorporated in the composition are flavouring substances known in the pharmaceutical field.

The suitable substances may be added to the enteric-coated proton pump inhibitor particles by mixing the different substances with the enteric-coated particles to a mixture or an ordered mixture. An ordered mixture may be produced for example by particle adhesion or coating processes.

The mixtures of enteric-coated proton pump inhibitor particles and the suitable constituents are dried before or after mixing to a moisture level where the proton pump inhibitor has a good long-term stability. The mixture is preferably dispensed into a tight applicator preferably in the form of a syringe.

The mixture of the enteric-coated proton pump inhibitor beads or tablets and other constituents can also comprise a suitable pH-buffering substance which will improve the functional stability of the formulation during its transport through the oesophagus and stomach before it reaches the small intestine where the proton pump inhibitor is dissolved and absorbed. Suitable buffering substances are citric acid, tartaric acid, succinic acid, malic acid, lactic acid, benzoic acid, sorbic acid and ascorbic acid and other substances. Such substances will decrease the pH-value of the gel produced to a value below 5.5, thus protecting the enteric coating of the beads or tablets.

Further the mixture of the enteric coated proton pump inhibitor particles and suitable constituents may also comprise inert particles, such as inert beads to facilitate the mixing of the different constituents with the enteric-coated particles. Such inert beads are for example beads of coated suger or any other kind of beads not harmful to the animal.

Enteric coated beads or tablets can be prepared by conventional methods. Enteric-coated pellets of omeprazole can for instance be prepared as described in the US Patent No. 4,786,505 (=EP 247983) hereby incorporated by reference in its entirety. Such enteric coated pellets or beads of omeprazole are preferably coated with at least two coatings one of which is an isolation coating/subcoat and the other is an enteric coating.

The preparation of a stable pharmaceutical composition according to the invention is performed by incorporating a proton pump inhibitor in the form of beads or tablets, which are coated with one ore more coatings one of which is an enteric-coating, into a paste-like gel.

More particular, the preparation of a formulation in the form of a paste-like gel is performed by either I) mixing the coated particles of the proton pump inhibitor with a dry gelling agent and optionally a pH-buffering system protecting the coated particles whereafter water is added ex tempore, just prior to administration to the animal, or II) mixing the coated particles with a potassium or calcium ion containing salt and optionally a pH-buffering system and thereafter ex tempore, just prior to administration to the animal, with a low-viscous water solution of a gelling agent such as a polymer compound or compounds or by III) mixing the coated particles ex tempore, just prior to administration to the animal, with a low-viscous solution of a gelling agent in the form of temperature-sensitive polymer and optionally with a pH-buffering system and then subjecting the mixture to gentle heating.

Examples

The omeprazole enteric-coated pellets in the examples below are prepared according to example 2 of US-A 4,786,505 (=EP 247983) hereby incorporated by reference in its entirety.

Example 1

Omeprazole enteric-coated pellets (corresponding to about 600 mg of omeprazole)	7 g
Xanthan gum	0.3 g

are mixed in a syringe.

When 10 ml of water are added a viscous gel is formed.

Example 2

Omeprazole enteric-coated pellets	7 g
Xanthan gum	0.3 g
Citric acid	60 mg

are mixed in a syringe.

When 10 ml of water are added a viscous gel is formed.

Example 3

Omeprazole enteric-coated pellets	7 g
Potassium chloride	30 mg

are mixed in a syringe.

When 10 ml of a 1% solution of kappa-carrageenan are added a viscous gel is formed.

Example 4

Omeprazole enteric-coated pellets	7 g

are dispensed into a syringe.

When 10 ml of a solution of EHEC (ethylhydroxyethylcellulose) 1.25% and sodium lauryl sulphate 0.1% are added and warmed to 35°C a viscous gel is formed.

Example 5

Lansoprazole enteric-coated pellets	10 g
(prepared according to examples 1 and 2 of EP 277 741, hereby incorporated by reference)	
(corresponding to lansoprazole ~900 mg)	
Xanthan gum	0.45 g
Citric acid	80 mg

When 15 ml of water are added a viscous gel is formed.

Example 6

Pantoprazole enteric-coated pellets	7 g
(prepared according to example 2 of EP 519 365, hereby incorporated by reference)	
(corresponding to pantoprazole ~1200 mg)	
Xanthan gum	0.3 g
Citric acid	50 mg

When 10 ml of water are added a viscous gel is formed.

The best mode of carrying out the invention known at present is to use the composition described in Example 2.

CLAIMS

1. A pharmaceutical composition for oral administration to animals comprising a proton pump inhibitor in the form of beads or tablets, which are coated with one or more coatings one of which is an enteric-coating, incorporated into a paste-like gel.

2. A pharmaceutical composition according to claim 1, wherein the beads or tablets are coated with at least two coatings one of which is a subcoat and the other is an enteric coating.

3. A pharmaceutical composition according to any of claims 1-2, wherein the pharmaceutical composition is intended for oral administration to horses.

4. A pharmaceutical composition according to any of claims 1-2, comprising components which are dry enteric-coated beads or tablets of a proton pump inhibitor, optionally mixed with dry constituents, which components on addition of water or a water solution gives a paste-like gel.

5. A pharmaceutical composition according to any of claims 1-2, comprising components which are dry enteric-coated beads or tablets of a proton pump inhibitor, dry gelling agent(s) and optionally pH-buffering and/or flavouring substances which components by the addition of water gives a paste-like gel.

6. A pharmaceutical composition according to any of claims 1-2, wherein dry enteric-coated beads or tablets of a proton pump inhibitor, dry gelling agent(s) and optionally pH-buffering and/or flavouring substances are mixed to a dry mixture before the addition of water of a water solution.

7. A pharmaceutical composition according to claim 6, wherein the mixture is an ordered mixture.

8. A pharmaceutical composition according to any of claims 1-2, comprising a first group of components which is dry enteric-coated beads or tablets of a proton pump inhibitor, a water soluble, organic or inorganic salt of potassium, calcium, magnesium or aluminium and optionally pH-buffering and/or flavouring substances, and a second group of components which is a water solution of a gelling agent, which groups of components when mixed give a paste-like gel.

9. A pharmaceutical composition according to any of claims 1-2, comprising a first group of components which is dry enteric-coated beads or tablets of a proton pump inhibitor, optionally mixed with dry pH-buffering and/or flavouring substances, and a second group of components which is a water solution of a temperature sensitive gelling agent, which groups of components when mixed and subjected to gentle heating give a paste-like gel.

10. A pharmaceutical composition according to claim 1, wherein the proton pump inhibitor is omeprazole.

11. A pharmaceutical composition according to claim 1, wherein the proton pump inhibitor is lansoprazole.

12. A pharmaceutical composition according to claim 1, wherein the proton pump inhibitor is pantoprazole.

13. A pharmaceutical composition according to claim 1, wherein the proton pump inhibitor is leminoprazole.

14. A stable pharmaceutical composition in the form of a kit comprising dry enteric coated beads of tablets of a proton pump inhibitor and dry consituents, which components on addition of water or a water solution give a paste-like gel.

15. A stable pharmaceutical composition in the form of a kit comprising a first group of components which is dry enteric-coated beads or tablets of a proton

pump inhibitor, a water soluble, organic or inorganic salt of potassium, calcium, magnesium or aluminium and optionally pH-buffering and/or flavouring substances, and a second group of components which is dry gelling agent(s), which groups of components when mixed in the presence of water give a paste-like gel.

16. A stable pharmaceutical composition in the form of a kit comprising a first group of components which is dry enteric-coated beads or tablets of a proton pump inhibitor, optionally mixed with dry pH-buffering and/or flavouring substances, and a second group of components which are temperature sensitive gelling agent(s), which groups of components when mixed in the presence of water and subjected to gentle heating give a paste-like gel.

17. A pharmaceutical composition according to any of the claims 1, 15 or 16 characterized in that the composition in its entirety or parts thereof is dispensed into an applicator in the form of a syringe.

18. A process for the preparation of a pharmaceutical composition according to claim 1, characterized by incorporating a proton pump inhibitor in the form of beads which are coated with one or more coatings one of which is an enteric-coating into a paste-like gel.

19. Use of a composition according to any of claims 1, 15 or 16 in the preparation of an active dosage form for the treatment of gastric acid related diseases in animals.

20. Method for treatment of gastric acid related diseases wherein a physiologically active amount of a composition according to claims 1, 15 or 16 is administered to an animal in the need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 94/00368

A. CLASSIFICATION OF SUBJECT MATTER

IPC : A61K 47/36, A61K 9/30, A61K 31/44
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC : A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE EMBASE WPI WPIL CLAIMS BIOSIS AGRICOLA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, A1, 8806893 (BENZON PHARMA A/S), 22 Sept 1988 (22.09.88), page 2, line 31 - page 4, line 8; page 7, line 25 - page 8, line 4; page 9, line 1 - line 25	1-19
A	EP, A2, 0496437 (AKTIEBOLAGET HÄSSLE), 29 July 1992 (29.07.92), page 3, line 35 - page 5, line 19, examples, claims	1-19
A	EP, A1, 519365 (BYK GULDEN LOMBERG CHEMISCHE), 23 December 1992 (23.12.92), page 2, line 34 - page 3, line 33, claims	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 1994	11 -08- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE94/00368

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 20
because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy methods (see PCT Rule 39(iv)).

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/94

International application No.
PCT/SE 94/00368

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 806893	22/09/88	NONE	
EP-A- 0496437	29/07/92	AU-B- 601974	27/09/90
		AU-A- 7191287	05/11/87
		CA-A- 1292693	03/12/91
		DE-A- 3783394	18/02/93
		EP-A,B- 0247983	02/12/87
		SE-T3- 0247983	
EP-A1- 519365	23/12/92	NONE	